DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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CBER-00-024

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

JUN 21 2000

WARNING LETTER

Certified Mail
Return Receipt Requested

Elliot J. Kopp, M.D.
C.A.R.E. Center
3320 Wake Forest Road
Raleigh, NC 27609

Dear Dr. Kopp:

During an inspection ending on April 7, 2000, Ms. Barbara M. Frazier, an investigator with the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study entitled

. submitted data from the clinical investigation to FDA in support of a Biologics License Application (BLA) Supplement. The inspection is part of FDA's Bioresearch Monitoring Program that includes inspections designed to audit the conduct of research involving investigational drugs.

The deficiencies noted during the inspection are listed on the Form FDA 483, Inspectional Observations, that was presented and discussed with you at the conclusion of the inspection (enclosed). Based on our review of the information from the inspection, we identified deviations from applicable federal regulations as published in Title 21, Code of Federal Regulations, Part 312 [21 CFR 312]. The applicable provisions of the CFR are cited for each violation.

1. **Failure to ensure that the investigation is conducted according to the signed investigational plan (protocol). [21 CFR 312.60]**

   Our inspection revealed protocol directives were not followed.

   a. At least four of 14 subjects received a different dose level from the specified/reported dose. For example:

i. Subject ——— appears to have received at least twice the reported dose of the test article throughout the study. The subject (weight = 122.7 kg) was assigned to group ——————— as shown by page 20.01 of the baseline part of the case report form (CRF) and the *Request for Patient Randomization and/or Drug Box Number(s)* form. The dose was calculated correctly at — ml of the study medication on the CRF. The vials contained — mls of test article. However, the *Dispensing/Accountability Records* show the subject used — vials over 164 days, nearly twice the number of vials required. You indicated that you called the subject's wife who explained that she injected the subject with — mls/day.

ii. Subject ——— appears to have received more than the reported dose of the test article throughout the study. The subject (weight = 108 kg) was assigned to group ——————— as shown by page 20.01 of the baseline part of the CRF and the *Request for Patient Randomization and/or Drug Box Number(s)* form. The dose was calculated correctly at — ml of the study medication on the CRF. However, the *Dispensing/Accountability Records* show the subject used — vials over 167 days, twice the number of vials required.

iii. Records for subject ——————— show the subject weighed 190 pounds on 7/16/96, more than 1.5 years prior to the study. The baseline weight on 3/18/98 for the subject was not done. The weight at screening on 3/11/98 was recorded as 263 pounds. The subject weighed 172 pounds at week 24 on 9/9/98. Two hundred sixty-three pounds was used to calculate the dose for the subject throughout the study, which appears to be approximately 1.5 times the appropriate dose for the subject.

iv. Records show subject——— (0.1 mg/kg/day) weighed 165 pounds (75 kg) at baseline. However, the weight was incorrectly entered as 75 pounds on the CRF, and the dose was incorrectly calculated as — mls, less than half the appropriate dose. The sponsor's monitor noted the error on 8/20/98. The subject continued on the erroneous dose until week 16 (9/25/98), when the dose was changed to the correct dose of — mls.

b. Two of 14 subjects did not meet protocol criteria regarding duration of ——— ——————————— . For example:

i. Records for subject ——— indicate the subject had ——————— since at least 1985. The subject entered the study in April 1998, more than 12 years post diagnosis. A 1995 ——— evaluation summary indicates the subject was 36 years old and had the disease for 10 years. A 1998 letter indicates the subject had the disease since she was 24 years old.

ii. A form to ——————————signed by you on 10/30/95 indicates subject ——— was diagnosed with ——————— in the spring of 1984, more than 12 years prior to study entry in May 1998.

2. Failure to maintain adequate records of disposition of the test article. [21 CFR 312.62(a)]

Drug accountability records at the site are not accurate. For example:

a. *Receiving and Dispensing Records* for the study were apparently not completed concurrently with study drug dispensing as evidenced by the grouping and recording of drug dispensation by subject number rather than by date. Therefore, the balance forward columns of the Dispensing Log are not accurate by date.

b. The records for boxes of the test article with serial numbers —— and —— are conflicting and confusing. For example:

i. *Receiving and Dispensing Records* do not show that these boxes (received on 6/25/98) were dispensed. However, the *Return Investigational Drug Record* dated 10/8/98 shows 17 used vials of —— and 11 used and 6 unused vials of —— were returned to the sponsor.

ii. The *Return Investigational Drug Record* shows a notation that the boxes were used by subject ——— , but the *Dispensing/Accountability Record* for the subject does not show these serial numbers being issued to the subject.

iii. The *Dispensing/Accountability Record* for subject ——— shows boxes —— and —— were dispensed to the subject. However, 6 used and 11 unused vials of —— are recorded. These numbers conflict with 11 used and 6 unused vials noted for box —— in the *Return Investigational Drug Record.*

3. Failure to prepare and maintain complete and accurate case histories. [21 CFR 312.62(b)]

There are data discrepancies and numerous corrections to CRFs and source documents. For example:

a. There is a lack of consistency for initial recording of data for joint counts, investigator's assessment of disease activity, or the subject's pain scales/health assessment questionnaires. Sometimes, source data was collected by recording directly onto the CRF pages. Other times, photocopies of the CRF pages were used to collect the original data that was later transcribed to CRF pages.

b. Subject ——— was the only subject at the site who had two versions of the Health Assessment Questionnaire (HAQ). In addition to the CRF version, a copy of the HAQ (Early Termination) was found in the office chart. However, the versions differed. The CRF version was marked "With MUCH difficulty" for " ——— ——— ?" The chart version (original) was marked "With SOME difficulty."

c. The adverse event report regarding an abnormal ECG for subject ——— in October 1998 was "corrected" after several data queries by the sponsor but erroneously reflects wording from the subject's abnormal ECG in April 1998. The October 1998 ECG indicates "probable anterior infarction." The April 1998 ECG indicates T-Wave Inversions and other non-specific ST/T abnormalities.

d. The inclusion criterion at screening for subject ——— in the CRF incorrectly indicates "Yes" to answer question number three regarding duration of the disease. The question asks if the duration of disease is > 6 months and < 8 years. Records show the subject was diagnosed in the spring of 1984, more than eight years prior to study entry.

e. Multiple corrections were made to records. There were numerous sponsor data queries regarding dates reported on CRF pages that did not match dates reported by the lab or inappropriate dates entered on CRF pages. For example:

   i. ——————— rate data were collected at the site, recorded on a form, and faxed to the sponsor. Two forms for subject ——— with collection dates of 10AUG98 and 03JUL98 show the following: one incorrect patient number not corrected, one incorrect year of birth not corrected, one patient number corrected, one patient initials corrected, one time of collection corrected, one visit week corrected, one collection day of the month corrected. In addition, the form for collection date of 30JUL98 for subject ——— shows the following corrections: patient number, initials, sex, date of birth, collection date, and time of collection.

   ii. The CRF for subject ——— at the week 4 visit (11/18/97) shows the subject's last (previous) injection date as 11/25/97.

We also noted that corrections to CRFs and source documents did not always show who made the changes and when the changes were made.

4. Failure to fulfill the general responsibilities of investigators. [21 CFR 312.60]

As evidenced by the deviations noted above, the records at your site indicate a serious failure to fulfill your responsibilities as principal investigator including supervision of study personnel. Staff who were delegated the authority to perform certain functions were not adequately trained and monitored. Although authority may be delegated, the principal investigator is ultimately responsible for study conduct. Please provide us with assurance that all study personnel, including the study coordinator(s) and sub-investigators, are trained in good clinical practices.

Deviations in the conduct of this study appear to be the result of your lack of understanding of the procedures and requirements that govern the use of investigational new drugs. Your signature on Form FDA 1572, Statement of Investigator, indicates your agreement to comply with all requirements regarding the obligations for clinical investigators conducting human clinical trials and all other pertinent requirements in 21 CFR Part 312. The commitment includes ensuring that you will conduct the study in accordance with the protocol and that adequate and accurate records of the study are maintained. Inspection results indicate that you did not follow the protocol, you did not maintain complete and accurate records, and you did not ensure adequate oversight of study personnel regarding recordkeeping requirements.

You are currently participating in five other clinical research studies. Non-compliance with the regulations governing the use of investigational drugs could affect not only the acceptability of the trial data but also the safety of the human subjects of research.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study. It is your responsibility to ensure adherence to each requirement of the law and applicable regulations.

Please notify this office in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step you plan to take to prevent a recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which corrections will be completed.

Failure to achieve prompt correction may result in enforcement action without further notice. These actions could include initiation of clinical investigator disqualification proceedings that may render a clinical investigator ineligible to receive investigational drugs, a clinical hold, or termination of an investigational new drug application (IND).

Please send your written response to:

Debra Bower (HFM-664)
FDA/Center for Biologics Evaluation and Research
Division of Inspections and Surveillance
1401 Rockville Pike
Rockville, MD 20852-1448

Please send a copy of your response to FDA's Atlanta District Office, Director, Compliance Branch, 60 Eighth St., NE, Atlanta, GA 30309. If you require additional time to respond, or have any questions concerning this matter, please contact Ms. Bower at (Tel.) 301-827-6221.

Sincerely,

for Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation
and Research

cc: _____